THE INJECTION AND INGESTION TEST IN CROSS-SENSITIZATION TO THE PARA GROUP

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Perutz, in his studies on pyrocatechol, developed the idea of hypersensitivity to a chemically well-defined group of substances. In France Flandin, Rabeau and Ukrainczyk (1) first called attention to the frequency of positive reactions to p-phenylenediamine in subjects who became sensitized by ointments containing synthetic local anesthetics. Nitti, Bovet and Depierre (2), while studying the reactions caused by aromatic amines, first considered the possibility of group sensitizations to compounds which are characterized by a primary amine in the para-position.

Before the French Dermatology Society (3) and the French Allergy Society (4) the present authors, on a number of occasions, have called attention to cross sensitizations to the para group. These sensitizations have become particularly frequent in France since the indiscriminate topical use of sulfonamide powder, especially of paraaminophenyl-sulfamide (1162F) which is certainly the most sensitizing of all the substances containing a paraamino group.

In addition to sulfonamides, paraphenylenediamine and the local anesthetics of the procaine type, there are other substances which belong to the same group and which have produced cross-reactions with paraphenylene-diamine, e.g. paraaminobenzoic acid (Meltzer and Baer (5) recently reported a cross-sensitization to glycerol paraaminobenzoate), paraaminosalicylic acid, certain rubbers and certain azodyes which are used for coloring nylon stockings (6) and medicaments and foods (7).

The conclusions of our previous studies, in which only patch tests were considered, were as follows: of the subjects who had developed dermatitis due to sulfonamides, 77% also reacted to paraphenylenediamine, 32% to sulfonamides and 32% to both paraphenylenediamine and sulfonamides. Of 54 subjects who had developed dermatitis due to paraphenylenediamine, 54% also reacted to procaine, 44% to paraaminophenylsulfonamide and 35% to both of these substances.

In the present paper we shall not deal with the reactions elicited by patch tests, but rather with those elicited by the ingestion or parenteral injection of the allergen in cases of hypersensitivity to the group of substances which have an amino group in the para position on the benzene ring.

INGESTION TESTS

1. Our first attempts with ingestion tests were made in cases dealing with subjects *who had a dermatitis due to sulfonamide*, with negative or doubtful

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Received for publication July 7, 1950.

patch test reactions. Once the eruption had cleared, we administered one-half gram tablet of paraaminophenylsulfamide to these patients. This procedure, at times, caused very serious reactions. In one of our previously published cases (8) the patient M12 developed syncope, a temperature of 40°C., delirium and an erythroderma (Table I). This patient was admitted to another hospital as an emergency case, a diagnosis of infectious erythroderma was made, and it was only due to the strenuous objection of the patient that administration of another large dose of sulfonamide was avoided. These extremely severe reactions, which occur after ingestion of sulfonamides in persons who have been sensitized through contact with sulfonamides, are well known. Yet one still not infrequently sees erythrodermas, purpuras, etc. after oral administration of sulfonamides in subjects who previously had had a contact dermatitis from sulfonamides, a fact which was not known to the treating physician because of an inadequately taken clinical history.

The next step was an investigation of whether the cross-sensitization to other compounds can be elicited by systemic, usually peroral, administration of the allergen.* This procedure was carried out in 25 cases, with positive reactions in 11 (Table I). In 6 of these 11 cases, the reaction was a local one, i.e., a recurrence of pruritus and an erythematovesicular eruption in previously affected sites. In 2 cases there was also spreading of the dermatitis beyond the originally involved sites. The reaction consisted only of diarrhea in case R121, a woman who was normally not suffering from this trouble. In 4 cases the reaction was both local and general with an elevation of temperature to 38°C. in the afternoon.

The following are other examples of the reactions encountered:

Patient R164 presented an eczematous eruption for eight days on the hands, face and ears. This had followed the application of a sulfonamide powder on a finger wound. The patch test with 1162F powder and with paraphenylenediamine was positive (it should be noted here that until then the patient had dyed her hair with no side effects). The ingestion of procaine brought about a temperature elevation to 38°C., an intense edematous eruption of the face and a pruritic eruption on the forearms, where previously no eruption had occurred. The patch test with procaine, which was subsequently done, was positive.

Patient R84 had eczema of the leg which followed treatment of a leg ulcer with sulfonamide powder. Patch tests were positive with paraphenylenediamine and paraaminophenylsulfamide. The ingestion of procaine brought on a temperature elevation to 38°C. and an intensely pruritic reaction at the former site of the leg eczema. The patch test with procaine, which was subsequently done, was positive.

Table I summarizes the cross-reactions to ingestion tests in the subjects with eczematous dermatitis due to sulfonamides.

*For this purpose we administered to all subjects who had sulfonamide eruptions as confirmed by patch tests, 0.10 gram of procaine by mouth (5 cc. of 2% solution) prior to the patch test with this substance.

2. Our second group of cases deals with subjects *who had become sensitized to ointments or solutions containing procaine, scuroforme, orthoform, etc. (i.e. local anesthetics with a primary amino group and substitution in the para position)*, with a positive patch test. Small quantities of paraaminophenylsulfamide (0.5 gram) were fed to patients with eczema due to topical application of local anesthetics (Table II). In the previously published (3) and very instructive case N8, there was eczema of the hands and wrists (Fig. 1) after topical application of an ointment containing procaine and scuroforme. Patch tests were positive (Fig. 2) and healing was complete a few days after use of the ointment was discontinued. One month later the patient was fed one tablet of 0.5 gram of 1162F. A veritable "explosion" followed with an intensely edematous and vesicular photosensitization dermatitis in all exposed areas. We wish to call attention to the fact that until then the face had been entirely free from involvement. The patient stated that he had never previously had contact with sulfonamides.

Of 10 cases which were tested in this way, 2 had a purely local reaction; in 1 case this was accompanied by spread of the eruption. In 5 cases, the reaction was both local and general. In 2 cases no reaction occurred.

Table II summarizes the results of these experiments. These experiments found further support in clinical findings illustrated by the two following cases:

One patient presented an eczema after application of an ointment containing scuroforme and procaine for a vulvar pruritus. Her physician then prescribed sulfadiazine for her. She took two such tablets and two days later a generalized eruption appeared. Patch tests were positive to procaine, paraaminophenylsulfamide, sulfadiazine and paraphenylenediamine.

Another patient had eczematous dermatitis of the nose and the upper lip after the use of nose drops containing stovaine and ephedrine. Ingestion of sulfadiazine tablets prescribed for this eruption provoked generalization of the eruption and a temperature rise to 38°C.

3. In *subjects with sensitization to paraphenylenediamine* with positive patch test we have also seen incidents after the ingestion of sulfonamides (0.5 gram of paraphenylsulfamide 1162F).

Patient P124 was a hairdresser with eczema of the hands and face. The patch test with paraphenylenediamine was positive but the test with paraaminophenylsulfamide was negative despite the fact that the patient had used a sulfonamide powder on his eczema. Ingestion of procaine caused no reaction, but ingestion of paraaminophenylsulfamide produced a temperature rise to 40°C. with reactivation of the lesions on the face, and generalization of the pruritus—and all this despite the negative patch test reaction to the sulfonamide.

Patient P49 presented an eczema of the scalp, eyelids and ears which developed after hair dyeing. The patch test with paraphenylenediamine was positive. Ingestion of procaine caused an extension of the dermatitis over the entire face, neck and the exposed part of the sternal region. Still, the patch test with procaine, which was done later on, did not produce a reaction.

Of 10 subjects with paraphenylenediamine dermatitis, the ingestion of pro-

TABLE I
Dermatitis due to Sulfonamides

SULFONAMIDE DERMATITIS (PATCH-TEST POSITIVE)		INGESTION TESTS (BEFORE PATCH-TEST)				INJECTION TEST	PATCH TESTS				
		Ingested Substance	Focal Reaction	Spreading	Generalized Reaction		Sulfonamide 1162 F	Procaine	P. phenylenediamine	P. amino Salicylic Acid	P. amino Benzoic Acid
M12	1162F powder	1162F	+	erythroderma	40° syncope		++				
N179	1162F powder	1162F	+	0	0		++	0	0		
065	1162F powder	procaine	0	0	0		+	+	+++		0
0124	1162F powder					procaine 0	++	++	±		
0141	1162F powder	1162F	++	generalized urticaria	37°5		++	+++	+++	+++	+++
0145	1162F powder	procaine	0	0	0		++	±	++		
0182	1162F powder	procaine	+	+	0		++	+	++	+	0
P2	1162F powder	procaine 1162F	+ +	0 +	0 0		++	++	+		
P16	1162F ointment	procaine 1162F	0 +	0 +	0 0	procaine 0	++		±		
P39	1162F powder	procaine	+	0	38°		++	+	+++	0	0
P52	1162F powder	procaine	0	0	0		++	±	+++		
P55	1162F powder	procaine	0	0	0		+++				
P74	(Sulfadiazine ingestion)	1162F	+	0	37°8		+	0	0	0	
P81	1162F powder	procaine	0	0	0		+++++	++	++++		0
P88	1162F powder	procaine	0	0	0		++	+	++++		
P103	1162F powder	PAS acid	0	0	headache hot flush		+++	++	++	+	0
P117	1162F ointment	procaine 1162F	0 +	0 0	0 0		++	0	++	++	0

P123	1162F powder	procaine PAS acid	0 0	0 0	0 headache		++	++	0	+	±
P169	1162F powder	procaine	+	0	0		+++	++	++++	++	0
P166	1162F powder	procaine PAS acid	0 0	0 0	0 0		++	++	+++	++	0
R61	1162F powder	procaine 1162F	0 +	0 0	0 39°		+	0	0		
R85	1162F powder	procaine 1162F	+ ++	0 +	38° 37°5		++	++++	+++		
R95	Fontamide ingestion	procaine 1162F	+ +	0 +	0 38°2		+	+	++	0	0
R121	1162F powder	procaine 1162F	0 0	0 0	diarrhea 0		++	0	0	0	0
R135	1162F powder	procaine 1162F	0 +	0 +	0 0		++	+++	++	0	0
R152	1162F powder	procaine	0	0	0		++	++	+	0	0
R156	sumedine ingestion	sumedine	+	+	37°8 headache		0	0	0		
R157	1162F powder	1162F	0	0	38°		+++	++	++++		
R164	1162F powder	procaine	+	+	38°2		++	++	+		
R182	1162F powder	procaine 1162F	0 +	0 0	0 38°2		+	0	+++	0	0
S26	1162F powder	procaine	+	0	0		++++		++		
S76	1162F ointment	procaine	+	pruritus generalized	0		++	0	+++		
S83	1162F powder	procaine	+	pruritus generalized	37°8		+	++	+++	0	0

TABLE II

Dermatitis due to Anesthetic ointments

LOCAL ANESTHETIC (PATCH-TEST POSITIVE)	INGESTION TESTS (BEFORE PATCH-TEST)				INJECTION TEST	PATCH TESTS				
	Ingested Substance	Focal Reaction	Spreading	Generalized Reaction		Procaine	1162 F	P. phenylenediamine	P. amino Salicylic Acid	P. amino Benzoic Acid
N8 procaine and scuroforme ointment	1162F	+	photosensitization	0		++	++	++++		
N186 procaine and scuroforme ointment	1162F	++	0	38°6		++	+++	++		
0155 scuroforme ointment	1162F	+	0	39°						
P26 percaine ointment	1162F	+	+	37°8		+	0	0	0	
P97 procaine and scuroforme ointment	1162F Procaine	0 0	0 0	0 0		++	0	++		0
P107 procaine and scuroforme ointment	1162F	+	generalization	38° nausea		+		++		
P11 8procaine liniment	1162F	+	0	0		+	++	++	++	++
P135 scuroforme ointment	1162F Procaine	0 0	0 0	0 0			0	++		
R174 scuroforme ointment	1162F	+	0	0		+	++	++		
S88 procaine and scuroforme ointment	1162F	+	generalization	40° syncope		+	++	++	+++	0

caine caused a local reaction at the previously involved site and local and general reaction in 1 case.

Of 14 subjects with paraphenylenediamine dermatitis, the ingestion of sulfonamides produced one local reaction and one general reaction. Table III summarizes the cross-reactions to ingestion tests in subjects with eczematous dermatitis due to paraphenylenediamine.

4. Finally, ingestion tests with procaine (0.10 gram diluted in 5 cc. of water) and paraaminophenylsulfamide (0.5 gram) were carried out in *subjects who presented reactions to other chemically related substances* such as those occurring in rubber, nylon stockings, tincture of arnica (11) and picric acid.

In patient S69, a woman who had a dermatitis due to rubber gloves with positive patch test to the rubber material and paraphenylenediamine, the ingestion of sulfonamides and procaine both brought about a temperature rise to 38°C. and 38.2°C. respectively, but no local flareup.

In patient S33, who presented a dermatitis due to the dyes in nylon stockings with positive patch tests to these stockings and to paraphenylenediamine, the ingestion of sulfonamides provoked a temperature rise to 38.8°C., a reactivation of the lesions with a spread to the forearms, the face and the sternal region which up to that time had been free from involvement.

Table IV summarizes the results of these tests.

The ingestion tests confirm what had already been demonstrated by analysis of certain clinical investigations: the possible dangers from sulfonamide therapy in subjects sensitized to substances containing the para amino group, i.e. one is not only dealing with a sensitization of sulfonamides, but often also to local anesthetics, paraphenylenediamine and certain related compounds. Baer, Leider and Mayer (7) have called attention to the existence of cutaneous group reactions between paraphenylenediamine and azodyes used for coloring foods and drugs in addition to those previously known with the azodyes in nylon stockings. The ingestion tests by Baer and Leider (9) and our own ingestion tests show that the cross-sensitizations extend also to elicitation by internal administration. Perhaps one can find here the explanation for the dermatitis in subjects with other sensitizations in this group.

INJECTION TESTS

On the basis of the understanding gained in the ingestion tests, a small number of cases were investigated to ascertain whether the cross-sensitization can be elicited also by parenteral administration of the allergen such as local anesthetics. In view of the frequency of administration of local anesthetics, this is a question of great practical importance.

The present authors have carried out testing by injection of procaine (1 cc. of 2% solution) in three cases. These tests were negative in two cases who had presented sulfonamide dermatitis. These are listed in Table 1 under O124 and P16.

Another case, P44, listed in Table III, which has been previously published (10), appears worthy of more detailed description. The patient was a hairdresser

TABLE III

Dermatitis due to p. phenylenediamine

CASES WITH POSITIVE PATCH-TEST	INGESTION TESTS				INJECTION TEST	PATCH TESTS				
	Ingested Substance	Focal Reaction	Spreading	Generalized Reaction		Sulfonamide 1162F	Procaine	P. phenylenediamine	P. amino Salicylic Acid	P. amino Benzoic Acid
N14 tailor (repairs dyed garments)	1162F	0	0	0	0		0	0	++++	
P44 hairdresser	1162F Procaine	0 +	0 0	0 0	Procaine: Local reaction with bulla, 40° syncope	+	++	+++		
P49 had hair dyed	1162F Procaine	0 +	0 Extension to decollete area	0 0		+	++	+++		
P61 hairdresser	1162F	0	0	0		0	+	++++		
P63 seamstress (repairs dyed garments)	1162F Procaine	0 0	0 0	0 0		0	0	+++		
P94 hairdresser	1162F Procaine	0 0	0 0	0 0		0	0	++		
P119 hairdresser	1162F Procaine	0 0	0 0	0 0		0	0	++	0	0
P124 hairdresser	1162F Procaine	+ 0	pruritus generalized 0	40° 0					++	0

P183 had hair dyed	Procaine	0	0	0		0	+	++		
R87 bis hairdresser	1162F Procaine	0 reactivation	0 0	0 38°			0	++		
R87 had hair dyed	1162F Procaine	0 +	0 0	0 0		0	0	++++		
R126 hairdresser	Procaine	+	+	0		0	0	++++	0	0
R171 had hair dyed	Procaine	+	0	38°5		0	+++	++++	0	0
S2 had hair dyed	1162F	0	0	0		0	0	++	0	0
S16 hairdresser	1162F Procaine	+ 0	+ 0	0 0		0	0	++	+	0

who had a lichenified patch on the anterior aspect of the left wrist. Patch tests were positive to paraphenylenediamine, but not to the cold wave liquid which the patient incriminated. The group reactions were positive to procaine and negative to paraaminophenylsulfamide. The ingestion of procaine caused a local flareup at the site of dermatitis. The patient, after following the precautions which she had been advised to take (rinsing with sodium chloride) was seen three months later; at that time she was greatly improved and able to continue her occupation. As she had to undergo a tooth extraction and was

TABLE IV

Dermatitis due to Substances Immunologically Related to P-phenylenediamine

CASES WITH POSITIVE PATCH TEST	INGESTION TESTS				INJECTION TEST	PATCH TESTS				
	Ingested Substance	Focal Reaction	Spreading	Generalized Reaction		Sulfonamide 1162F	Procaine	P. phenylen-diamin	P. amino Salicylic Acid	P. amino Benzoic Acid
0156 rubber dermatitis	1162F	+	+	0			+	++		
0174 rubber dermatitis	Procaine	+	+	0		+	0	++		
P110 rubber dermatitis	Procaine	+	0	0		0	0	0	0	0
P137 rubber dermatitis	1162F Procaine PAS	+ 0 0	0 0 0	0 0 0		0	0	+++	+++	0
P138 rubber dermatitis	1162F	0	0	0				+		
S69 rubber dermatitis	1162F Procaine	0 0	0 0	38° 38°2			++	++		
S33 nylon stocking dermatitis	1162F	+	+	38°8			++	+++	0	0
R131 Tincture of arnica	1162F	+	0	37°6		++	0	+++		
S27 Picric acid	1162F	0	0	0						

aware of the dangers which procaine held for her, she was willing to undergo an injection test. One cc. of a 2% solution of procaine was injected in the area of the left wrist under the lichenified plaque which had persisted slightly. The patient immediately became pale, her pulse was thready and she complained of nausea, malaise and choking. There was also a recurrence of intense pruritus at the sites of the patch test which had been done several weeks before. In the afternoon there was a temperature rise to 38°C. with an edematous eruption on the face and a vesicular eczema on the dorsum of the hand along an area where procaine had run down during the injection. During the night a bulla

appeared on the wrist and a slough at the injected site. Finally there developed a dyshidrotic eruption on the previously uninvolved hand. The malaise lasted for 48 hours, after which time all signs and symptoms disappeared gradually. Nevertheless, another incident occurred. Inadvertently the patient applied a procaine containing liniment to a burn and this was followed by the appearance of a patch of eczematous dermatitis at the site. It should be noted that during previous years, the patient was able to have tooth extractions under local anesthesia without untoward occurrences. Apparently the procaine sensitivity became manifest only after the onset of the occupational hair dye dermatitis. The sensitization was established by the cutaneous route but manifestations could be elicited by contact, injection and parenteral administration and was both local and systemic. One can imagine the disastrous accidents that could have occurred if a larger quantity of procaine had been injected for local anesthesia on the gums.

The following clinical observations show that the cutaneous sensitization can be elicited by parenteral administration as well.

A woman presented an eczematous dermatitis of the back of the hand which came on after local infiltration for incision of a panaritium. The patch test with procaine and with paraphenylenediamine was positive. The previous history of the patient, who had worked with a dentist, showed that she had developed itchy eruptions every time she had handled procaine and that these eruptions forced her to give up her work.

In another woman who had been treated with procaine infiltrations for varicose ulcers, a purpuric eruption appeared at the site. The patch test was positive.

Group reactions were observed clinically in still other cases. A patient presented a dermatitis of the face and neck after dyeing a dress herself. Three years previously, the use of sulfonamide powder had caused an eczema of the legs and thighs, an eczema which recurred two years later after she received an injection of thiodacaine.

A furrier had a generalized dermatitis for two years with positive tests to paraphenylenediamine and paraaminophenylsulfamide which had been used locally. A year before he was seen by us, local anesthesia for a tooth extraction had produced a state of syncope and chills and the next day a generalized eruption.

A patient presented a generalized eruption due to paraaminophenylsulfamide powder. The patch test was positive. His previous history indicated that he had had eruptions on and off for 15 years. The group reaction tests showed a positive reaction to procaine. After this had been called to the patient's attention it was found that all his eruptions had followed tooth extractions under local anesthesia.

Another patient who had become sensitized to 1162F powder, developed a temperature rise to 39°C. after a procaine injection for a sprained ankle.

Still another patient who had become sensitized to contact with sulfonamides, went into shock after ingestion of a sulfonamide and developed syncope after local anesthesia for a tooth extraction.

Obviously procaine injections represent a real danger in subjects with sensitization to the para group. They can be responsible not only for cutaneous manifestations, but also for potentially severe shock.

CONCLUSIONS

Cutaneous sensitization can bring about systemic sensitizations and occasionally serious accidents that can be caused by the agent which has sensitized the patient, as well as by an entire group of chemically related substances. Among these substances the sulfonamides and the local anesthetics are perhaps the most dangerous because of the possible consequences of systemic administration, i.e. either by ingestion or by injection.

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